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Mesencephalic corticospinal atrophy predicts baseline deficit but not response to uni- or bilateral arm training in chronic stroke

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Abstract

Objective: Stroke survivors with motor deficits often have pyramidal tract atrophy caused by degeneration of corticospinal fibres. It is hypothesized that the degree of atrophy correlates with deficit severity in chronic stroke state and predicts the response to rehabilitation training.

Methods: A post-hoc analysis of 42 chronic stroke survivors (> 6 months) randomized to either 6 weeks of bilateral arm training (BATRAC) or dose-matched therapeutic exercises (DMTE) were performed. Arm function was measured using the Fugl-Meyer (FM) and modified Wolf Motor Function Test (WMFT). Structural MRI was obtained to assess corticospinal tract (CST) atrophy by planimetric measurement of the mesencephalon (mesencephalic atrophy ratio, MAR). Fractional anisotropy (FA) was measured using diffusion tensor imaging (DTI) on the pontine level. Voxel-based lesion symptom mapping (VLSM) was used to determine the lesions associated with highest degrees of atrophy. The predictive value of CST atrophy on deficit and training response was analyzed.

Results: CST atrophy predicted baseline motor arm function measured by FM and WMFT (FM: $r=0.39$, $p=0.014$; WMFT: $r=-0.35$, $p=0.042$), while there was only a trend for the correlation with FA ($p<0.1$). No measure of atrophy predicted response to either BATRAC or DMTE. CST atrophy was higher with larger lesions ($r=-0.50$, $p=0.035$) and those that affected the CST ($r=-0.49$, $p=0.038$). VLSM identified internal capsule lesions as being associated with highest CST atrophy ($p<0.01$).

Conclusion: Larger lesions, internal capsule lesions and those overlapping the pyramidal tract are associated with greater CST atrophy. CST atrophy explains in

part the variability of baseline deficits but does not seem to predict the response to BATRAC or unilateral arm training.

Introduction

Several rehabilitation techniques have proven effectiveness in stroke survivors even years after stroke [1-4]. Because therapy response is variable, there is a growing need for measures that predict the response of the individual subject.

Bilateral arm training with rhythmic auditory cueing (BATRAC) is one therapy that improves arm function in some but not all subjects with chronic upper extremity deficits [2, 5-7]. Patients are trained for 6 weeks performing rhythmic movements with both arms.

We hypothesized that therapy response is poor in subjects with marked corticospinal tract atrophy. Atrophy and morphological changes of the cerebral peduncles caused by Wallerian and transsynaptic degeneration of pyramidal tract fibres are often observed in chronic stroke survivors [8-12]. Wallerian degeneration (WD) is characterized by progressive degeneration of the distal portion of the injured axon and consecutively by degeneration of the myelin sheath and removal of myelin debris. While WD occurs fast in the peripheral nervous system (PNS) (within days to weeks), it is very slow (months to years) and incomplete in central nervous system (CNS) of mammals. Rapid clearance of myelin seems to result in an extracellular environment that promotes axon regeneration in the PNS, whereas in the CNS, the prolonged presence of myelin-associated inhibitors likely contributes to the failure of CNS axons to regenerate and consecutively leads to atrophy (for review see [13]. Because this process is very slow it may lead to a slowly progressive deterioration of function even long after a stroke. Preventing this decline is an important therapeutical target.

Magnetic resonance imaging (MRI) can be used to determine the degree of atrophy and the structural integrity of the corticospinal tract (CST). A recent study showed

that the degree of mesencephalic pyramidal tract atrophy is a function of the extent of CST injury in the lesioned hemisphere [10]. Similarly, Warabi et al. [14] had observed a positive relationship between descending motor tract injury and the mesencephalic CST atrophy in chronic stroke. The same investigators later found evidence that patients with CST atrophy greater than 60% showed limited recovery of hand function [15]. But, reports on the relationship between CST atrophy and therapy response or deficit severity remain controversial [16-21].

Diffusion tensor imaging (DTI) is an MRI technique often used to evaluate CST integrity by measuring the amount of directional diffusion of protons along white matter tracts (fractional anisotropy, FA). Two studies showed a correlation between DTI measures of CST atrophy, motor evoked potentials (MEP) as a measure of functional CST integrity and arm function in chronic stroke survivors [20, 22].

Additionally, Stinear and colleagues reported poor improvements after a 30-day upper extremity rehabilitation program in patients who had a high degree of CST damage on DTI (FA asymmetry index > 0.25) and absent MEPs [20, 22].

Here, several neuroimaging methods were combined to assess the relationship between CST atrophy, motor deficits at baseline and response to bilateral arm training (BATRAC) and unilateral arm training (DMTE). Voxel-based lesion symptom mapping (VLSM) was used to identify lesions that are associated with severe CST atrophy [23]. CST atrophy and integrity was determined by DTI and morphologically by measuring midbrain symmetry on axial MRI sections [14].

Material & Methods

Study participants

This report presents a post-hoc analysis of a single-centre, randomized, controlled trial comparing BATRAC and dose-matched therapeutic exercises (DMTE; unilateral arm training based on conventional physiotherapy) in their effects on arm function (Whitall et al, submitted). We analyzed 42 subjects that had undergone MRI scanning at baseline. Seventeen were in the BATRAC and 17 in the DMTE group. Eight participants dropped out during training after receiving baseline assessments and MRI scanning. Reasons for dropping out were medical complications, personal or social issues, and difficulty with transportation to the training site. While all subjects received anatomical MRI scans, DTI was acquired in 23 subjects. The remaining participants did not tolerate the additional scan time of DTI. Two DTI scans had to be excluded from the analysis because of movement artefacts.

Subjects were enrolled in the trial if they had residual upper extremity hemiparesis following a single ischemic stroke equal or longer than 6 month prior to enrolment. All patients had the ability to initiate antigravity shoulder/elbow movement in flexion and extension in the transverse plane such that at least 3 inches of forward movement occurred. All participants had completed 3 to 6 months of conventional rehabilitation therapy. Inclusion criteria included adequate language and cognitive function to understand instructions. Patients with multiple clinical strokes, a history of other neurological disease, chronic pain, or emotional disorders were excluded. The study was conducted as part of the University of Maryland School of Medicine, National Institute on Aging– Claude D. Pepper Older Americans Independence Center in collaboration with the Division of Brain Injury Outcomes, Johns Hopkins University. All study participants provided written informed consent. The study was approved

from the ethics committees of the participating institutions (the University of Maryland School of Medicine, the Baltimore Veterans Affairs Medical Center, and the Johns Hopkins University School of Medicine).

BATRAC Training

BATRAC training consisted of hour-long therapy sessions (four 5-minute movement periods interspersed with 10-minute rest periods) 3 times per week for 6 weeks. Upon auditory cues at individually determined preferred rates of 0.67 to 0.97 Hz, participants pushed and pulled bilaterally, in synchrony or alternation, two T-bar handles sliding in the transverse plane. The control group received dose matched unilateral therapeutic exercise (DMTE) for the upper extremities over the same time period. DMTE involved 4 exercises based on neurodevelopmental principles [24], including thoracic spine mobilization, scapular mobilization, weight bearing with the paretic arm, and opening the hand with finger extension performed on the same 5-minute schedule as BATRAC. This treatment emphasizes handling techniques that facilitate body and limbs to assume “normal” positions. Participants were encouraged to actively move while performing the exercises. Participants were aware of the treatment differences, but did not know that DMTE was a control intervention; thus, subjects reasonably expected an improvement regardless of group.

Assessments of impairment and function

Upper extremity motor function was measured with the upper-extremity portion of the Fugl-Meyer Motor Performance Test (FM) [25] and the modified Wolf Motor Function Test [26] (WMFT). The mean time, which was required to perform the 14 tasks of the WMFT with the paretic arm and hand, was used in statistical analyses. Maximum time allowed for each task was 120 seconds. Assessments were conducted at a location separate from the training site and carried out by a tester (same person each

time) blinded to group assignment.

MRI Data Acquisition and Analysis

MRI scanning was performed with a 1.5 T scanner (Philips, Eindhoven, Netherlands) at the Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, USA. Scanning was performed within two weeks before the start of training.

A T1-weighted sequence (3D-MPRAGE sequence; resolution $1 \times 1 \times 1 \text{ mm}^3$, whole brain coverage) was used to measure the mesencephalic asymmetry ratio (MAR) and to characterize lesion location and size. The MAR was used to quantify CST atrophy at the level of the mesencephalon. The sizes of the left and the right mesencephalon were measured planimetrically on an axial slice. The axial slice was parallel to the plane through the mamillary body and the posterior commissure. The axial slice was positioned mid-way between mamillary body and upper rim of the pons. Planimetric measurements were conducted using Medical Image Processing, Analysis and Visualization software (MIPAV, Version 3.1.6; [27]). MAR was defined as the ratio of affected to unaffected side.

Voxel- Based Lesion- Symptom Mapping (VLSM)

For Voxel-Based Lesion-Symptom Mapping (VLSM) [23] T1-weighted images were transformed into Talairach space [28] by rotation and scaling using Brain Voyager QX software (Brain Innovation BV, Maastricht, The Netherlands). Binary lesion masks were produced based on T1-weighted scans by manually segmenting the lesion area. Areas of CSF intensity and hypodense regions at the boundary were combined to define the lesion. Lesion size was derived from the lesion mask by multiplying the number of voxels with voxel volume (1 mm^3). Manual segmentation

was performed using MRICro (Chris Rorden, University of Nottingham, Great Britain). Masks with right-hemisphere lesions were flipped so that the lesion was always on the left. The binary lesion masks of each subject were entered into the voxel-based lesion symptom mapping software (VLSM, <http://crl.ucsd.edu/vlsm>, based on Matlab, Mathworks Inc., Natick, MA, USA). For each of these voxels, subjects were divided into two groups, whether or not that voxel was included in the lesion mask. To keep the number of subjects in those groups sufficient for statistical comparisons, only voxels that were part of three or more lesion masks were considered. The MAR values for both groups were then compared using t-tests resulting in a t-value for each voxel. The colour-coded map of the t-values of all voxels was then overlaid onto a healthy brain template using a threshold of $p \leq 0.05$. Brain regions with significant t-values were localized using the Talairach daemon [29].

Assessment of direct CST injury

To measure the degree of CST injury the overlap of each stroke lesion with the CST was determined counting the number of common voxels in the lesion mask and a CST region of interest (ROI). The CST ROI was obtained from a DTI-based fibre tract atlas in Talairach space [30]. In addition to the absolute number of common voxels, the percent overlap was calculated as the quotient between common voxel number and the number of all voxels in the CST ROI.

Diffusion tensor imaging (DTI)

DTI data were acquired using a single-shot, echo-planar imaging (EPI) sequence with sensitivity encoding (SENSE, parallel-imaging factor of 2.5 [31]). The imaging matrix was 96 X 96 with a field-of-view of 240 x 240 mm (nominal resolution, 2.5 mm), zero-filled to 256 X 256 pixels. Transverse sections of 2.5 mm thickness were acquired parallel to the anterior commissure-posterior commissure line. A total of 50-

55 sections covered the entire brain and brainstem without gaps. Diffusion weighting was encoded along 30 independent orientations [32], and the b-value was 700 s/mm². Five additional images with minimal diffusion weighting ($b \approx 33$ s/mm²) were also acquired. To enhance the signal-to-noise ratio, this protocol was repeated three times. Fractional anisotropy (FA) of pontine corticospinal tract fibres was measured to assess CST integrity as described in detail elsewhere [33]. The FA ratio was built between FA of unlesioned and lesioned CST. To allow for a comparison with other studies [e.g. 20], lateralization indices were also calculated for FA (difference over the sum ((FA unlesioned – FA lesioned) / FA unlesioned + FA lesioned)).

Statistical analyses

To assess therapy response general linear models were used to predict the change in outcome variables (FM, WMFT) across time (difference post-pre), one for each variable. Independent variables included group (comparison BATRAC vs. DMTE) and the baseline value of the respective dependent variable. Additionally within group comparisons were (paired t-test; difference in test performance: post- – pre- training) were conducted for each group. General linear modeling was used to determine lesion parameters associated with CST atrophy and to analyze the predictive value of lesion and atrophy parameters for baseline deficit and therapy response. Separate models were computed for each dependent variable, CST atrophy, baseline WMFT, baseline FM, change in WMFT and change in FM over the training period.

Independent variables were CST atrophy (MAR, for baseline deficit and therapy response models), lesion size, lesion location (cortical versus subcortical), time since stroke, age and CST damage (overlap between lesion and CST). Separate models were computed to test the influence of FA on the dependent variables, because DTI data was only available in a subset of patients. Independent variables were entered

and removed from the models in a stepwise fashion using $p < 0.25$ as entry and then $p > 0.05$ as a criterion for removal. Interactions were included in the model and removed if insignificant. Data are expressed as mean \pm standard deviation. A 2-tailed $p < 0.05$ was considered significant.

Results

The results of the parent randomized-controlled trial about the efficacy of BATRAC therapy versus DMTE will be reported elsewhere. Briefly, significant improvements in FM and modified WMFT were shown for both groups without between group differences. Basic demographic and clinical characteristics of the study participants are provided in Table 1. While all patients included here underwent FM testing (n=42), WMFT scores were only available in 36 patients. In the present sample of 34 patients (BATRAC/DMTE= 17/17) in which MRI scans as well as baseline and post-training functional data were available, there was a significant improvement in WMFT in the BATRAC group (-2.9 ± 2.4 s; range: +3.6 to -12.9 s; $t=2.79$; degrees of freedom (df)=16; $p=0.01$) and a trend of improved function in FM score for BATRAC ($+0.94 \pm 2.9$ points; range: -2 to +5; $t=-1.36$; df=16; $p=0.19$) and in both FM and WMFT in DMTE ($+1.3 \pm 3$; range: -3 to 5; $t=-1.77$; df=16; $p=0.1$ respectively -3.0 ± 5.3 s; range: +1.8 – 13.0 s; $t=-1.9$; df=10; $p=0.1$). Repeated measures ANOVA revealed no significant time-by-group interactions for both measures (FM: $F(1,32)=0.12$; $p=0.73$; WMFT: $F(1,26)=0.001$; $p=0.98$) (see table 1).

Lesion profiles predicting CST atrophy

In addition to a correlation between CST damage (overlap CST-lesion) and lesion size (cortical: $r=0.73$, $p=0.0001$; subcortical: $r=0.89$, $p<0.0001$), both variables independently predicted CST atrophy, i.e., MAR (size: $r=-0.50$, $p=0.035$, CST overlap: $r=-0.49$, $p=0.038$, **Figure 1**). Both factors together explained 31% of the variability of MAR. Interactions between lesion size, CST damage and lesion location (cortical versus subcortical) were insignificant and removed from the model. Lesion location, age and time since stroke did not explain the variability of MAR. For those

subjects in whom DTI was available, FA-ratio did not correlate significantly with MAR ($r=0.1$).

VLSM analysis was used to identify lesion patterns that were associated with CST atrophy ($n=42$). VLSM can only identify those brain regions that are lesioned in 3 or more subjects in the sample. Within this compound brain area (**Figure 2A**) lesions in the internal capsule were statistically related to higher degree of ipsilesional CST atrophy ($t=2.522$, $p<0.01$) (**Figure 2B**).

CST atrophy, baseline function and therapy response

High CST atrophy predicted low arm function (baseline FM score: $r=0.39$; $p=0.014$, WMFT time: $r=-0.35$, $p=0.042$, **Figure 3**). FA was not significantly related to baseline arm function but trends were noted for both baseline FM score (ratio: $r=0.4$, $p=0.06$; lateralisation index: $r=-0.41$, $p=0.051$) and baseline WMFT (ratio: $r=-0.43$, $p=0.09$; lateralisation index: $r=0.46$, $p=0.08$). No parameter characterizing lesion morphology (size, location, CST overlap) and atrophy (MAR, FA) predicted therapy response in the BATRAC, DMTE groups or in all subjects combined.

Discussion

CST atrophy measured at the level of the mesencephalon occurs with larger cortical or subcortical lesions affecting the CST. While chronic upper extremity motor deficits are associated with high degrees of CST atrophy, atrophy does not influence response to BATRAC or DMTE in chronic stroke survivors.

Warabi et al. [14] reported an association between lesion size and location and mesencephalic atrophy in 89 chronic stroke survivors. Mark et al. [10], however, did not find infarct size to predict atrophy in their sample of 34 chronic stroke survivors but reported that CST atrophy was related to the degree of overlap CST damage (CST-lesion overlap) as we observed in our sample. Consistent with this observation is the VLSM analysis that identified lesions in the internal capsule, i.e., subcortical lesions strategically affecting the CST, to be specifically prone to produce CST atrophy. Our data also show a relationship between the size of cortical strokes and CST atrophy (**Figure 2A**) indicating that large cortical lesions also cause atrophy. It has to be mentioned, that one limitation of planimetric measurement of mesencephalic peduncular atrophy is, that it does not encompass the CST exclusively and results might be influenced by degeneration of other corticofugal tracts as well.

Larger lesions themselves seem to be associated with more severe deficits in the acute phase as well as three months after stroke [34-38]. Some reports, including ours in chronic stroke however, have not found this relationship [39, 40]. Certainly, lesion location influences the size-deficit relationship. Direct correlations may only exist as long as lesions within the same functional brain system are compared [15, 36, 38, 41]. For example, it is known from clinical practice that even larger lesions affecting or extending into frontal areas may be clinically silent, at least if patients are

not intensively tested neuropsychologically. Therefore, the combination of size and location (“lesion profile”) may be required to determine deficits and prognosis [35, 37].

Although the lesion profile did not predict deficit severity here, CST atrophy did. This observation is in accordance with the results of two recent studies [20, 22]. However, the conclusion that atrophy causes arm impairment is premature, because disuse of the arm as a consequence of the initial deficit may have contributed to CST atrophy.

No lesion or atrophy parameter predicted response to BATRAC or DMTE. One previous report showed less benefit from a 30-day unilateral upper extremity training program including active and passive practices in chronic stroke survivors with greater CST damage determined by DTI and dysfunction assessed using transcranial magnetic stimulation (TMS) [20]. Differences in clinical baseline impairment and the degree of CST disintegration – subjects in the study of Stinear et al. had markedly lower baseline FM scores (16 ± 7.3 vs. 31.9 ± 12.5) and greater CST damage than our subjects – may explain contrasting results. Stinear et al. reported predictive effects only for patients in whom no MEPs were evoked by transcranial magnetic stimulation. Those patients showed an FA lateralization index > 0.25 and did not improve at all. We cannot exclude that a similar association exists in a subset of our patients as we have no MEP data and only 3 patients (13%) had an FA index > 0.25 . Thus, it may be that only severe atrophy may negatively affect therapy response. The benefit of rehabilitation therapies may additionally be determined by the ability of the non-lesioned brain to undergo functional reorganization or neuroplasticity [5]. Consequently, factors predicting therapy response may be found in unaffected rather than lesioned brain at least for bilateral training. Alternatively,

reorganization may involve cortical and subcortical networks that exclude the mesencephalon.

Fractional anisotropy showed only a trend towards an association with motor deficits. This may either be the consequence of low statistical power due to a small sample or may reflect methodological limitations, e.g., DTI being very sensitive to motion artefacts.

In conclusion, this study suggests that larger lesions and those that affect the CST are associated with severe CST atrophy at the level of the mesencephalon. CST atrophy predicts deficit severity in chronic stroke survivors. CST atrophy seems to have no negative effect on bilateral or unilateral rehabilitation training, which is reassuring for this highly affected group of individuals.

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Table 1. Baseline characteristics and therapy response				
	BATRAC (n=17)	DMTE (n=17)	ALL (n=42)	p-value
Age (years)	60.6±13.7	56.2±14.6	60.4±14.1	0.37 ¹
Gender (f/m)	9/8	10/7	22/20	0.73 ²
Time since stroke (months)	45.3±37.9	47.5±43.6	44.4±38.1	0.88 ¹
Stroke Side (left/right)	7/10	7/10	16/26	1.0 ²
Location:				0.72 ²
Cortical	9	7	22	
Subcortical	7	8	16	
Brainstem	1	2	4	
MAR	0.8±0.14	0.78±0.17	0.81±0.15	0.7 ¹
FA ratio	0.81±0.18	0.74±0.12	0.77±0.16†	0.26 ¹
FA lateralisation index	0.1±0.1	0.16±0.1	0.13±0.1†	0.16 ¹
Functional scores (Baseline)				
FM	31.9±12.5	28.3±12.4	32.5±12.9	0.4 ¹
WMFT (time; s)	52.6±38.7	56.6±38.0	48.3±36.8	0.8 ¹
Functional change**			(n=34)	
FM	0.94±2.9	1.3±3	1.1±2.9	0.73 ³
WMFT (time; s)	-2.9±2.4*	-3.0±5.3	-2.95±4.7	0.98 ³

¹ between group comparison (t-test; BATRAC vs. DMTE)

² Fisher Exact Test

³ MANOVA (time*group interaction; BATRAC vs. DMTE)

† N=23

* within group comparison (paired-T) significant by p<0.05)

** Functional change= therapy response as defined by the difference of scores: post – pre training

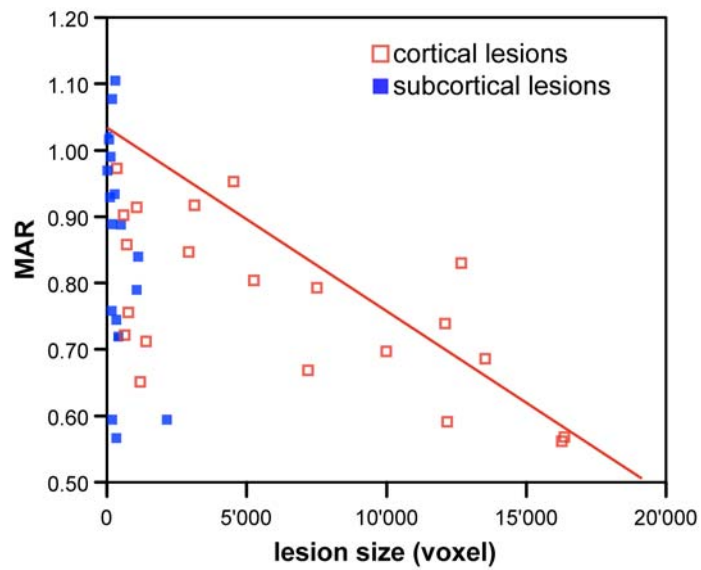


Figure 1. Relationship between lesion size and mesencephalic atrophy ratio (MAR) for cortical and subcortical lesions in all subjects (n=42). Lower MAR values indicate higher degrees of atrophy.

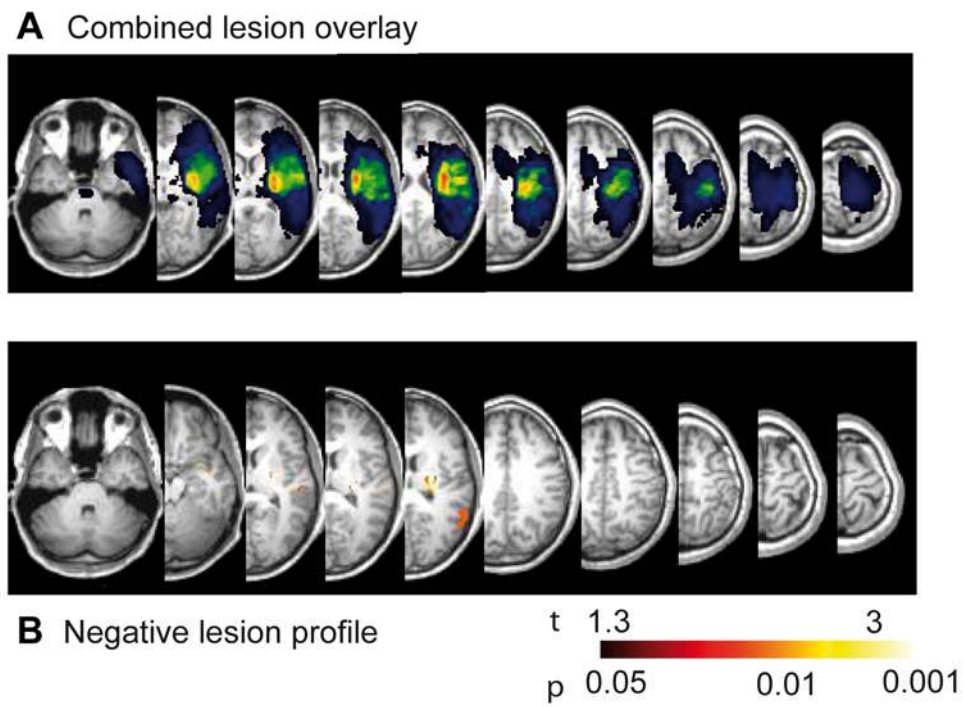


Figure 2. (A) overlay of all lesions included in the sample (n=42), (B) voxels predicting high degrees of CST atrophy ($p < 0.01$).

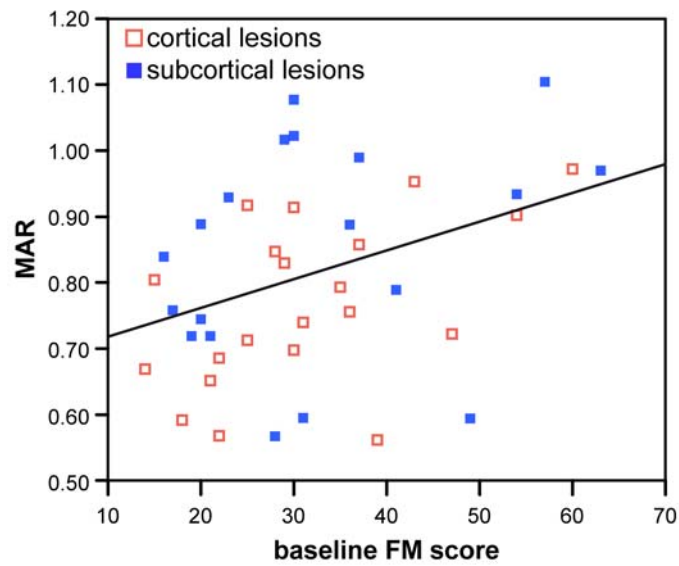


Figure 3. Correlation between arm function and CST atrophy in all subjects (n=42). Lower MAR values, i.e. higher atrophy, are associated with lower FM scores, i.e. lower arm function.